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Cell surface tagging and a suicide mechanism in a single chimeric human protein.

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Human gene therapy (UNITED STATES) Nov 1 1999, 10 (16) p2651-5, ISSN 1043-0342 Journal Code: 9008950
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Many therapeutic uses of gene-modified cells could benefit from inclusion of a surface marker for immunoselecting transduced cells. Another desired feature is a failsafe mechanism to ablate engineered cells if required. We describe here a system that combines a cell surface tag and an inducible apoptosis mechanism in a single protein. Spencer et al. (Curr. Biol. 1996;6:839-847) described an inducible cell suicide gene containing a myristoylation sequence, the human protein FKBP12, and the intracellular domain of Fas. Cells expressing this protein apoptose on treatment with a cell-permeable chemical dimerizing agent that binds two FKBP domains and cross-links the chimeric Fas proteins. We modified this system by anchoring a Fas-FKBP construct to the membrane with the extracellular and transmembrane domains of the low-affinity nerve growth **factor receptor** (LNGFR), thereby uniting cell surface tagging with the inducible apoptosis mechanism. Cells retrovirally transduced with this construct apoptosed on exposure to a chemical dimerizer, AP1903 (Clackson et al., Proc. Natl. Acad. Sci. U.S.A. 1998;95:10437-10442). The LNGFR-tagged construct showed an unpredicted clear advantage over the myristoylation-anchored construct in its efficiency of signaling in HT1080 cells. This linked marker and failsafe mechanism may have particularly attractive safety properties for gene therapy. The use of gene-modified cells in basic research and clinical studies is enhanced by the use of a selectable surface marker for immunoselection of transduced cells. Another desired feature for gene and cell therapies is an inducible suicide system to eliminate transduced cells when necessary. Spencer et al. (Curr. Biol. 1996;6:839-847) described a potential failsafe mechanism whereby exposure of cells to a chemical dimerizing agent activates the Fas-mediated apoptotic pathway. In this system, the intracellular signaling domain of Fas is linked to one or more copies of the human protein FKBP12. Treatment of engineered cells with a cell-permeable chemical dimerizing agent that simultaneously binds to two **FKBP** domains cross-links the **chimeric** Fas protein and induces apoptosis. Here, we modify the system by anchoring a Fas-FKBP construct to the membrane with the extracellular domain of the low-affinity nerve growth **factor receptor** (LNGFR), to unite cell surface tagging of transduced cells with the inducible apoptosis mechanism. Cells retrovirally transduced with this construct undergo apoptosis on exposure to a chemical dimerizer, AP1903. A linked marker and failsafe mechanism may have particularly attractive safety properties for gene therapy.

Small-molecule control of insulin and PDGF receptor signaling and the role of membrane attachment.

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BACKGROUND: Receptor tyrosine kinases (RTKs) regulate the proliferation, differentiation and metabolism of cells, and play key roles in tissue repair, tumorigenesis and development. To facilitate the study of RTKs, we have made conditional alleles that encode monomeric forms of the normally heterotetrameric insulin receptor and monomeric platelet-derived growth **factor** (PDGF) beta **receptors** fused to the FK506-binding protein 12 (FKBP12). The chimeric receptors can be induced to undergo dimerization or oligomerization by a small synthetic molecule called FK1012, and the

consequences were studied in cells and embryonic tissues. RESULTS: When equipped with an amino-terminal plasma membrane localization sequence and expressed in HEK293 cells, these chimeric receptors could signal to downstream targets as indicated by the FK1012-dependent activation of p70 S6 kinase (p70(S6k)) and mitogen-activated protein (MAP) kinase. In Xenopus embryos, the engineered PDGF receptor protein induced the formation of mesoderm from animal-pole explants in an FK1012-dependent manner. A cytosolic variant of the protein underwent efficient transphosphorylation, yet failed to activate appreciably either p70(S6k) or MAP kinase following treatment with FK1012. These results provide evidence of a requirement for membrane localization of RTKs, consistent with current models of RTK signaling. CONCLUSION: We have developed an approach using the small molecule FK1012 to conditionally activate **chimeric** proteins containing **FKBP** **fused** to the insulin receptor or to the PDGF beta receptor. Using this system, we were able to induce mesoderm formation in Xenopus animal-cap tissue and to demonstrate that membrane localization is required for RTK signaling in transfected cells. This system should allow the further dissection of RTK-mediated pathways.

FK1012 growth Ldb+

Redesigning an FKBP-ligand interface to generate chemical dimerizers with novel specificity.

Clackson T; Yang W; Rozamus L W; Hatada M; Amara J F; Rollins C T; Stevenson L F; Magari S R; Wood S A; Courage N L; Lu X; Cerasoli F; Gilman M; Holt D A

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Apoptosis

FKBP ligand homodimers can be used to activate signaling events inside cells and animals that have been engineered to express fusions between appropriate signaling domains and FKBP. However, use of these dimerizers in vivo is potentially limited by ligand binding to endogenous FKBP. We have designed ligands that bind specifically to a mutated FKBP over the wild-type protein by remodeling an FKBP-ligand interface to introduce a specificity binding pocket. A compound bearing an ethyl substituent in place of a carbonyl group exhibited sub-nanomolar affinity and 1,000-fold selectivity for a mutant FKBP with a compensating truncation of a phenylalanine residue. Structural and functional analysis of the new pocket showed that recognition is surprisingly relaxed, with the modified ligand only partially filling the engineered cavity. We incorporated the specificity pocket into a **fusion** protein containing **FKBP** and the intracellular domain of the Fas **receptor** . Cells expressing this modified chimeric protein potently underwent apoptosis in response to AP1903, a homodimer of the modified ligand, both in culture and when implanted into mice. Remodeled dimerizers such as AP1903 are ideal reagents for controlling the activities of cells that have been modified by gene therapy procedures, without interference from endogenous FKBP.

FKBP/FasR AP1903

Controlling programmed cell death with a cyclophilin-cyclosporin-based chemical inducer of dimerization.

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cyclophilin/FasR
md.CsA → apoptosis

BACKGROUND: Cell death can occur either from physical damage (necrosis) or cellular suicide (apoptosis). Apoptosis is essential for the development

of multicellular organisms and disregulated apoptosis underlies many human diseases. The Fas **receptor** (Fas) is a membrane signaling protein that mediates a death signal following its aggregation by the Fas ligand. We have described methods to induce the association of proteins using cell-permeable molecules called chemical inducers of dimerization (CIDs). Here we describe the synthesis of a novel CID, (CsA)2, that has two identical protein-binding surfaces derived from the immunosuppressant cyclosporin A (CsA). We use this CID to deliver a death signal to cells expressing a **fusion** protein containing **cyclophilin** (CyP, the protein **receptor** for cyclosporin) and the cytoplasmic signaling domain of Fas. RESULTS: (CsA)2 was synthesized in six synthetic steps and 30% overall yield from cyclosporin. It binds to two CyP proteins simultaneously, but does not inhibit T-cell signaling, presumably because the (CsA)2-CyP complex does not bind to calcineurin. Jurkat cells stably transfected with constructs encoding myristoylated CyP-Fas fusion proteins undergo apoptosis in response to nanomolar quantities of (CsA)2. Constructs containing a mutation in the myristoylation signal are defective for signaling. CONCLUSIONS: The Fas signaling pathway can be activated with a cell-permeable CID derived from CsA in cells expressing an appropriately engineered Fas construct, which must be localized at the membrane. This new class of homodimerizing CIDs will be useful for in-depth analysis of protein association events in complex systems, including transgenic animals. Now that several CIDs with distinct dimerization characteristics are available, it should be possible to induce the activation of multiple pathways with complete specificity.

Dexamethasone negatively regulates the activity of a chimeric dihydrofolate reductase/glucocorticoid receptor protein.

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A chimeric gene was constructed encoding the entire murine dihydrofolate reductase (DHFR) protein with a carboxyl-terminal extension encompassing amino acids 494-795 of the rat glucocorticoid **receptor** (GR). The **chimeric DHFR** /GR gene encoded a functional DHFR protein, as measured by the ability to transform DHFR-deficient Chinese hamster ovary (CHO) cells to a DHFR-positive phenotype. The DHFR/GR protein bound [3H]dexamethasone with a similar affinity as wild-type GR. Selection of stable CHO transformants in increasing concentrations of methotrexate resulted in increased expression of DHFR/GR. Addition of dexamethasone, a synthetic glucocorticoid agonist, decreased the activity of the chimeric protein, as measured by colony formation in selective medium, binding of fluoresceinated methotrexate, and direct enzymatic assay for DHFR. Addition of RU486, a glucocorticoid antagonist, antagonized the effect of dexamethasone. In the absence of dexamethasone, the chimeric protein was primarily localized to the cytoplasm. In the presence of dexamethasone or RU486, DHFR/GR translocated into the nucleus. However, RU486 did not decrease DHFR activity, distinguishing subcellular location from functional activity. These results demonstrate that glucocorticoids negatively affect the function of DHFR/GR.

Title: Small-molecule control of insulin and PDGF receptor signaling and the role of membrane attachment (ABSTRACT AVAILABLE)

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Abstract: Background: Receptor tyrosine kinases (RTKs) regulate the proliferation, differentiation and metabolism of cells, and play key roles in tissue repair, tumorigenesis and development. To facilitate the study of RTKs, we have made conditional alleles that encode monomeric forms of the normally heterotetrameric insulin receptor and monomeric platelet-derived growth factor (PDGF) beta receptors fused to the FK506-binding protein 12 (FKBP12). The chimeric receptors can be induced to undergo dimerization or oligomerization by a small synthetic molecule called FK1012, and the consequences were studied in cells and embryonic tissues,

Results: When equipped with an amino-terminal plasma membrane localization sequence and expressed in HEK293 cells, these chimeric receptors could signal to downstream targets as indicated by the FK1012-dependent activation of p70 S6 kinase (p70(S6k)) and mitogen-activated protein (MAP) kinase, In Xenopus embryos, the engineered PDGF receptor protein induced the formation of mesoderm from animal-pole explants in an FK1012-dependent manner. A cytosolic variant of the protein underwent efficient transphosphorylation, yet failed to activate appreciably either p70(S6k) Or MAP kinase following treatment with FK1012, These results provide evidence of? a requirement for membrane localization of RTKs, consistent with current models of RTK signaling.

Conclusion: We have developed an approach using the small molecule FK1012 to conditionally activate **chimeric** proteins containing **FKBP fused** to the insulin **receptor** or to the PDGF beta **receptor** . Using this system, we were able to induce mesoderm formation in Xenopus animal-cap tissue and to demonstrate that membrane localization is required for RTK signaling in transfected cells, This system should allow the further dissection of RTK-mediated pathways.

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CROSS-REFERENCE TO RELATED APPLICATIONS This application is a continuation of U.S. Ser. No. 09/087,811, filed May 29, 1998 (U.S. Pat. No. 6,054,436), which is a continuation of U.S. Ser. No. 08/292,597,

filed Aug. 18, 1994 (U.S. Pat. No. 5,834,266), which is a continuation-in-part of Ser. No. 08/179,143 filed Jan. 7, 1994 (abandoned), which is a continuation-in-part of Ser. No. 08/093,499 filed Jul. 16, 1993 (abandoned); and a continuation-in-part of Ser. No. 08/196,043 filed Feb. 11, 1994 (abandoned), which is a continuation-in-part of Ser. No. 08/179,748 filed Jan. 7, 1994 (abandoned), which is a continuation-in-part of Ser. No. 08/092,977 filed Jul. 16, 1993 (abandoned), which is a continuation-in-part of Ser. No. 08/017,931 filed Feb. 12, 1993 (abandoned). The contents of each of these applications is hereby incorporated by referenced into the present disclosure. The full contents of related cases PCT/US94/01617, PCT/US94/01660 and PCT/US94/08008 are also incorporated by reference into the present disclosure.

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ART-UNIT: 166

PRIMARY-EXAMINER: Schwartzman; Robert A.

ABSTRACT:

We have developed a general procedure for the regulated (inducible)
dimerization or oligomerization of intracellular proteins and disclose methods
and materials for using that procedure to regulatably initiate cell-specific
apoptosis (programmed cell death) in genetically engineered cells.

18 Claims, 35 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 34

US-PAT-NO: 6187757
DOCUMENT-IDENTIFIER: US 6187757 B1

TITLE: Regulation of biological events using novel compounds

DATE-ISSUED: February 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Clackson; Timothy P.	Cambridge	MA	N/A	N/A
Gilman; Michael Z.	Newton	MA	N/A	N/A
Holt; Dennis A.	Royersford	PA	N/A	N/A
Keenan; Terence P.	Cambridge	MA	N/A	N/A
Rozamus; Leonard	Bedford	MA	N/A	N/A
Yang; Wu	Plainsboro	NJ	N/A	N/A

ASSIGNEE INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
ARIAD Pharmaceuticals, Inc.	Cambridge	MA	N/A	N/A	02

APPL-NO: 09/ 012097

DATE FILED: January 22, 1998

PARENT-CASE:

This application is a continuation in part of U.S. Ser. No. 08/791,044, filed Jan. 28, 1997, which itself is a continuation in part of U.S. Ser. No. 08/481,941 (filed Jun. 7, 1995, now abandoned) and claims the benefit of U.S. Ser. No. 60/015,502 (filed Feb. 9, 1996) and is a continuation in part of

International Application No. PCT/US96/09948 (filed internationally Jun. 7, 1996).

INT-CL: [07] A61K031/70,C12N005/10

US-CL-ISSUED: 514/31;435/325 ;435/355 ;435/372 ;435/372.3 ;435/375

US-CL-CURRENT: 514/31; 435/325 ; 435/355 ; 435/372 ; 435/372.3 ; 435/375

FIELD-OF-SEARCH: 435/325; 435/355 ; 435/372 ; 435/372.3 ; 435/375 ; 514/31 ; 536/6.5

REF-CITED:

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PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
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5604234	February 1997	Or	
N/A	N/A	N/A	
5658776	August 1997	Flotte	
N/A	N/A	N/A	
9101616	November 1998	Clackson et al.	
N/A	N/A	N/A	

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U.S. application No. 09/101,616, Clackson et al., filed

Nov. 2, 1998.

ART-UNIT: 166

PRIMARY-EXAMINER: Schwartzman; Robert A.

ABSTRACT:

Materials and methods are disclosed for regulation of biological events such as target gene transcription and growth, proliferation or differentiation of engineered cells.

54 Claims, 6 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 5

US-PAT-NO: 6077947
DOCUMENT-IDENTIFIER: US 6077947 A

TITLE: DNA encoding an intracellular chimeric receptor comprising Janus kinase

DATE-ISSUED: June 20, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Capon; Daniel J.	Hillsborough	CA	N/A	N/A
Tian; Huan	Cupertino	CA	N/A	N/A
Smith; Douglas H.	Foster City	CA	N/A	N/A
Winslow; Genine A.	Hayward	CA	N/A	N/A
Siekevitz; Miriam	New York	NY	N/A	N/A

ASSIGNEE INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
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APPL-NO: 08/ 485598

DATE FILED: June 7, 1995

PARENT-CASE:

This application is a continuation application of application Ser. No. 08/382,846, filed Feb. 2, 1995, which is now abandoned.

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5470730	November 1995	Greenberg et al.	435/172.3
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5504000	April 1996	Littman et al.	435/194
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ABSTRACT:

The present invention is directed to novel chimeric proliferation receptor proteins and DNA sequences encoding these proteins where the chimeric proteins are characterized in three general categories. In one category, the novel chimeric proteins comprise at least three domains, namely, an extracellular inducer-responsive clustering domain capable of binding an extracellular inducer that transmits a signal to a proliferation signaling domain, a transmembrane domain and a proliferation signaling domain that signals a host cell to divide. In the second category, the novel chimeric proteins comprise at least two domains, namely, an intracellular inducer-responsive clustering domain capable of binding an intracellular inducer and a proliferation signaling domain that signals the cell to divide. In yet a third category, a novel hybrid chimeric protein receptor is contemplated that contains an intracellular or extracellular inducer domain, a transmembrane domain, a proliferation signaling domain and an effector signaling domain in a single chain molecule. Whether the binding domain is intracellular or extracellular, the binding of inducer to these novel chimeric receptor proteins induces the clustering of the binding domains to each other and further signals the cell to proliferate, and optionally, signal an effector function. The present invention further relates to expression vectors containing the nucleic acids encoding the novel chimeric receptors, cells expressing the novel chimeric receptors and therapeutic methods of using cells expressing these novel receptors for the treatment of cancer, infectious disease and autoimmune

diseases, for example.

14 Claims, 4 Drawing figures

Exemplary Claim Number: 1

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08/093,499 filed Jul. 16, 1993, abandoned, this case is also a continuation-in-part of Ser. No. 08/196,043 filed Feb. 14, 1994, abandoned, which is a continuation-in-part of Ser. No. 08/179,748 filed Jan. 7, 1994, abandoned, which is a continuation-in-part of Ser. No. 08/092,977 filed Jul. 16, 1993, abandoned, which is a continuation-in-part of Ser. No. 08/017,931 filed Feb. 12, 1993, abandoned. The contents of each of these applications is hereby incorporated by referenced into the present disclosure. The full contents of related cases PCT/US94/01617, PCT/US94/01660 and PCT/US94/08008 are also incorporated by reference into the present disclosure.

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by cyclosporin A." PNAS 90:148.

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Peptidylprolyl Isomerases, and Blockade of T Cell Signal Transduction" The

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Zydowsky, et al. (1992) "Active site mutants of human cyclophilin: A separate peptidyl-prolyl isomerase activity from cyclosporin A binding and calcineurin inhibition" Protein Science 1:1092.

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ART-UNIT: 166

PRIMARY-EXAMINER: Elliott; George C.

ASSISTANT-EXAMINER: Schwartzman; Robert

ABSTRACT:

We have developed a general procedure for the regulated

(inducible)
dimerization or oligomerization of intracellular proteins
and disclose methods
and materials for using that procedure to regulatably
initiate cell-specific
apoptosis (programmed cell death) in genetically engineered
cells.

64 Claims, 35 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 34

US-PAT-NO: 5994313
DOCUMENT-IDENTIFIER: US 5994313 A

TITLE: Regulated apoptosis

DATE-ISSUED: November 30, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Crabtree; Gerald R.	Woodside	CA	N/A	N/A
Schreiber; Stuart L.	Cambridge	MA	N/A	N/A
Spencer; David M.	Los Altos	CA	N/A	N/A
Wandless; Thomas J.	Cambridge	MA	N/A	N/A
Belshaw; Peter	Somerville	MA	N/A	N/A

ASSIGNEE INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Board of Trustees of the Leland S. Stanford, Jr. Univ.	Stanford	CA	N/A	N/A	02
President and Fellows of Harvard College	Cambridge	MA	N/A	N/A	02

APPL-NO: 08/ 483898

DATE FILED: June 7, 1995

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS This application is a divisional of U.S. Ser. No. 08/292,597, filed Aug. 18, 1994 (now U.S. Pat. No. 5,834,266), which is a continuation-in-part of U.S. Ser. No. 08/179,143, filed Jan. 7, 1994, (now abandoned) which in turn is a

continuation-in-part of
U.S. Ser. No. 08/093,499, filed Jul. 16, 1993 (now abandoned). U.S. Ser.
No. 08/292,597 is also a continuation-in-part of U.S. Ser. No. 08/196,043,
filed Feb. 14, 1994 (now abandoned), which in turn is a continuation-in-part
of U.S. Ser. No. 08/179,748, filed Jan. 7, 1994 (now abandoned), which in
turn is a continuation-in-part of U.S. Ser. No. 08/092,977, filed Jul. 16,
1993 (now abandoned), which in turn is a continuation-in-part of U.S. Ser.
No. 08/017,931, filed Feb. 12, 1993 (now abandoned).

INT-CL: [06] A61K031/70,A61K038/13 ,A61K048/00 ,C12N005/10

US-CL-ISSUED: 514/31;424/93.21 ;435/325 ;435/372.3 ;514/9

US-CL-CURRENT: 514/31; 424/93.21 ; 435/325 ; 435/372.3 ; 514/9

FIELD-OF-SEARCH: 435/69.1; 435/325 ; 435/375 ; 435/7.1 ; 435/372.3 ; 552/502
; 514/169 ; 514/9 ; 514/10 ; 514/14 ; 514/31 ; 800/2 ; 424/93.21

REF-CITED:

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PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
5171671	December 1992	Evans et al.	435/69.1
	N/A	N/A	
5589362	December 1996	Bujard et al.	435/69.1
	N/A	N/A	

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FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
23550	November 1993	WO	

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Synthesis of the C.sub.17 -C.sub.25 Fragment"; J. Org. Chem. 51:5032-5036
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ART-UNIT: 166

PRIMARY-EXAMINER: Elliott; George C.

ASSISTANT-EXAMINER: Schwartzman; Robert

ABSTRACT:

We have developed a general procedure for the regulated (inducible)
dimerization or oligomerization of intracellular proteins and disclose methods
and materials for using that procedure to regulatably initiate cell-specific
apoptosis (programmed cell death) in genetically engineered cells.

48 Claims, 32 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 34

US-PAT-NO: 5741899
DOCUMENT-IDENTIFIER: US 5741899 A

TITLE: Chimeric receptors comprising janus kinase for regulating cellular pro
liferation

DATE-ISSUED: April 21, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Capon; Daniel J.	Hillsborough	CA	N/A	N/A
Tian; Huan	Cupertino	CA	N/A	N/A
Smith; Douglas H.	Foster City	CA	N/A	N/A
Winslow; Genine A.	Hayward	CA	N/A	N/A
Siekevitz; Miriam	New York	NY	N/A	N/A

ASSIGNEE INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Cell Genesys, Inc.	Foster City	CA	N/A	N/A	02

APPL-NO: 08/ 481003

DATE FILED: June 7, 1995

PARENT-CASE:

This application is a continuation of application Ser. No. 08/382,846, filed
Feb. 2, 1995, which is pending.

INT-CL: [06] C12N015/62,C12N005/10 ,C07K019/00 ,C07K014/705

US-CL-ISSUED: 536/23.4;435/69.7 ;435/320.1 ;435/325 ;435/377 ;530/350
;530/387.3

US-CL-CURRENT: 536/23.4; 435/320.1 ; 435/325 ; 435/377 ; 435/69.7 ; 530/350
; 530/387.3

FIELD-OF-SEARCH: 536/23.4; 435/69.7 ; 435/240.2 ; 435/320.1 ; 435/325 ; 435/377
; 530/387.3 ; 530/350

REF-CITED:

U.S. PATENT DOCUMENTS

PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
5359046	October 1994	Capon et al.	536/23.4
	N/A	N/A	
5470730	November 1995	Greenberg et al.	435/172.3
	N/A	N/A	
5504000	April 1996	Littman et al.	435/194
	N/A	N/A	

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FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
0340793	August 1989	EP	
WO9319163	September 1993	WO	
WO9429438	December 1994	WO	

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ART-UNIT: 182

PRIMARY-EXAMINER: Walsh; Stephen

ASSISTANT-EXAMINER: Pak; Michael D.

ABSTRACT:

The present invention is directed to novel chimeric proliferation receptor proteins and DNA sequences encoding these proteins where the chimeric proteins

are characterized in three general categories. In one category, the novel chimeric proteins comprise at least three domains, namely, an extracellular inducer-responsive clustering domain capable of binding an extracellular inducer that transmits a signal to a proliferation signaling domain, a transmembrane domain and a proliferation signaling domain that signals a host cell to divide. In the second category, the novel chimeric proteins comprise at least two domains, namely, an intracellular inducer-responsive clustering domain capable of binding an intracellular inducer and a proliferation signaling domain that signals the cell to divide. In yet a third category, a novel hybrid chimeric protein receptor is contemplated that contains an intracellular or extracellular inducer domain, a transmembrane domain, a proliferation signaling domain and an effector signaling domain in a single chain molecule. Whether the binding domain is intracellular or extracellular, the binding of inducer to these novel chimeric receptor proteins induces the clustering of the binding domains to each other and further signals the cell to proliferate, and optionally, signal an effector function. The present invention further relates to expression vectors containing the nucleic acids encoding the novel chimeric receptors, cells expressing the novel chimeric receptors and therapeutic methods of using cells expressing these novel receptors for the treatment of cancer, infectious disease and autoimmune diseases, for example.

12 Claims, 16 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

US-PAT-NO: 5614397
DOCUMENT-IDENTIFIER: US 5614397 A

TITLE: Method and compositions for modulating lifespan of hematolymphoid cells

DATE-ISSUED: March 25, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Weissman; Irving	Redwood City	CA	N/A	N/A
Lagasse; Eric	Palo Alto	CA	N/A	N/A

ASSIGNEE INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Board of Trustees of the Leland Stanford Junior University	Stanford	CA	N/A	N/A	02

APPL-NO: 08/ 200016

DATE FILED: February 22, 1994

INT-CL: [06] C12N015/85,C12N005/10

US-CL-ISSUED: 435/172.3;435/325 ;435/355

US-CL-CURRENT: 435/458; 435/325 ; 435/355

FIELD-OF-SEARCH: 435/240.2; 435/240.21 ; 435/172.3 ; 514/44 ; 424/93.21

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
WO93/25683	December 1993	WO	

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mutagenesis, " Nature (1992) 359:211-215.

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Chronic Granulomatous Disease," Blood (1992) 79:829-1835.

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chronic granulomatous disease by bone marrow transplantation," Bone Marrow
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in Neutrophil Specific Granule Deficiency," J. Clin. Invest. (1989) 83:514-519.

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Apoptosis, Polycystic Kidneys, and Hypopigmented Hair," Cell (1993) 75:229.

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ART-UNIT: 185

PRIMARY-EXAMINER: Ketter; James S.

ABSTRACT:

Methods and compositions for modifying the lifespan of progeny cells of
mammalian hematopoietic stem cells, particularly myeloid series cells, are
provided. Transgenic nonhuman mammals also are provided which produce

transgenic myeloid cells having an altered lifespan.

10 Claims, 20 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 16